Sotalol-induced bradycardia reversed by glucagon

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SUMMARY

Glucagon is considered the drug of choice for treating bradycardia and hypotension encountered during β-blocker poisoning. Its potential usefulness in reversing adverse effects encountered during therapeutic dosing with β-blockers has not been well characterized. We present a case of sotalol-induced bradycardia reversed by glucagon.

RÉSUMÉ

Le glucagon est accepté comme médicament de choix pour traiter la bradycardie et l'hypotension associées à l'intoxication aux β-bloquants. Les caractéristiques de son efficacité potentielle à renverser les effets secondaires indésirables que pose le dosage thérapeutique des β-bloquants ne sont pas encore bien définies. Nous présentons un cas de bradycardie provoquée par le sotalol et renversée par le glucagon.

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BETA-BLOCKING AGENTS ARE USED to treat a variety of medical disorders including angina, essential hypertension, supraventricular and ventricular tachycardias, thyrotoxicosis, migraine, and post–myocardial infarction.[1] Adverse effects directly related to β-adrenoreceptor blockade are reported for approximately 10% of patients and include congestive heart failure, bradycardia, bronchospasm, hypoglycemia, intermittent claudication, and Raynaud's phenomenon.[2] Although the use of glucagon in the treatment of β-blocker overdoses has been described,[3-6] its effectiveness in reversing adverse effects encountered during therapeutic use is not well characterized.

Case report

An 80-year-old woman came to the emergency department with a 1-day history of episodic lightheadedness. She denied syncope, chest pain, dyspnea, vomiting, or diarrhea. Her medical history showed thyroiditis requiring partial thyroidectomy and subsequent secondary hypothyroidism. She had a 10-year history of stable angina, and 2 months before admission, she had had an episode of paroxysmal atrial fibrillation following cataract surgery.

The patient had been given sotalol (80 mg twice daily) to prevent further recurrences. This dose of sotalol had not been adjusted since her last visit, and she denied ingesting excess medication. There was no history of renal or liver disease. Additional medications at the time of presentation included levothyroxine (0.1 mg daily), enteric-coated salicylic acid (325 mg daily), and sublingual nitroglycerin as needed.

On examination, the patient appeared pale but in no obvious distress. Initial vital signs in the supine position showed a heart rate of 42 beats/min, blood pressure of 122/60 mm Hg, respirations 20 breaths/min, and temperature 36.4°C. In an upright position, heart rate was 52 beats/min and blood pressure was 160/80 mm Hg.

Head and neck examination revealed a thyroidectomy scar. Jugular venous pressure was normal, and there were no carotid bruits. The chest examination was clear, and cardiac examination showed normal heart

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sounds with a 2/6 systolic crescendo-decrescendo murmur at the apex, radiating to the axilla. The abdomen was soft, and there was no peripheral edema. Results of neurologic examination were completely normal.

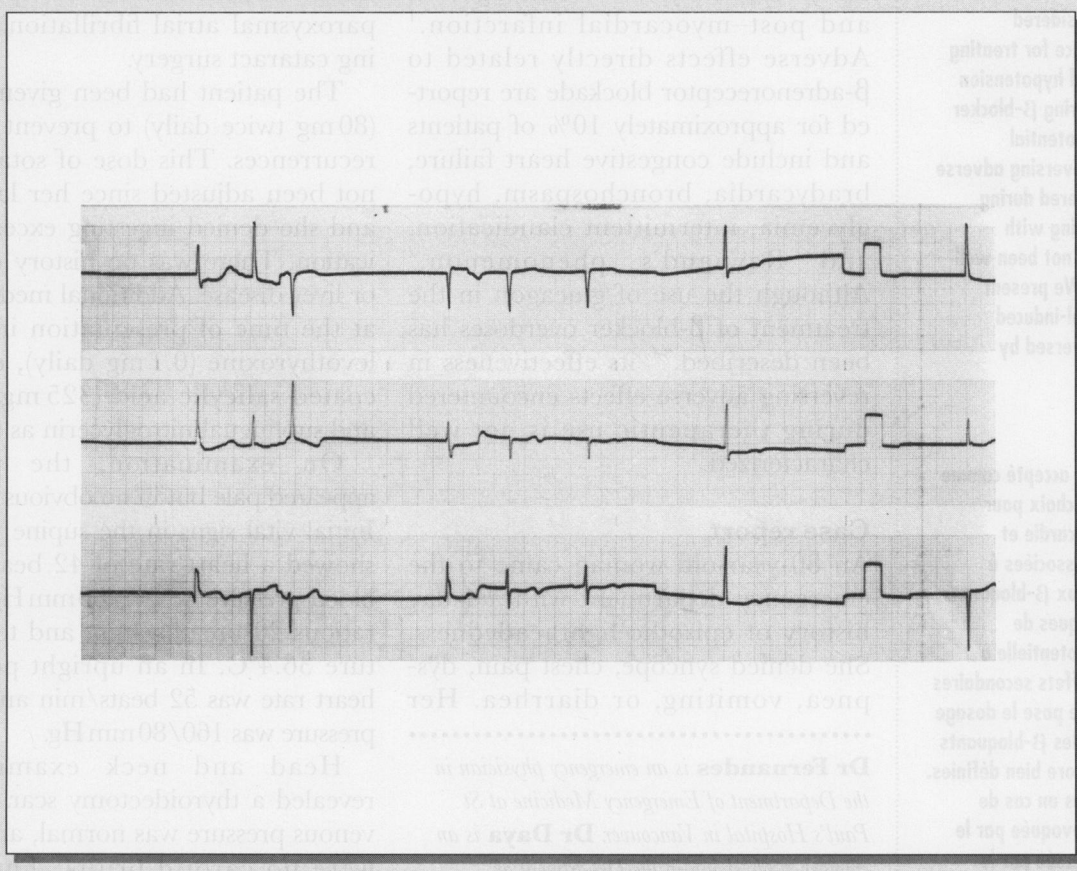
Results of complete blood count were normal. Serum sodium level was 139 mmol/L; potassium, 4.4 mmol/L; chloride 105 mmol/L; bicarbonate, 28 mmol/L; blood urea nitrogen, 8.7 mmol/L; creatinine, 131 mmol/L; and glucose, 6.6 mmol/L. Cardiac enzyme levels were normal.

The initial rhythm strip (*Figure 1*) demonstrated an irregular rhythm with a rate of 30 to 80 beats per minute. There were periods of sinus arrest, interspersed with junctional escape beats and sinus bradycardia.

The possibility of sotalol-induced symptomatic bradycardia was considered, and glucagon was administered at a rate of 0.2 mg/min. After 3.5 mg was administered, the rhythm converted to a normal sinus with a rate of 60 beats/min. The subsequent electrocardiogram (*Figure 2*) showed sinus rhythm with ST depression and T wave inversion in leads V_2 through V_6 with a QT interval of 0.44 seconds and a QT_c interval of 0.43 seconds. The patient's blood pressure remained stable at 140/70 mm Hg.

The patient was admitted to the coronary care unit for further monitoring. She experienced one episode of nausea and vomiting. In the unit, she received an additional 15 mg of glucagon over the next 5 hours for sporadic asymptomatic episodes of sinus arrest. There were no further episodes of sinus arrest, and the patient remained stable in a sinus

Figure 1. **Lead II rhythm strip obtained on presentation to the emergency department**



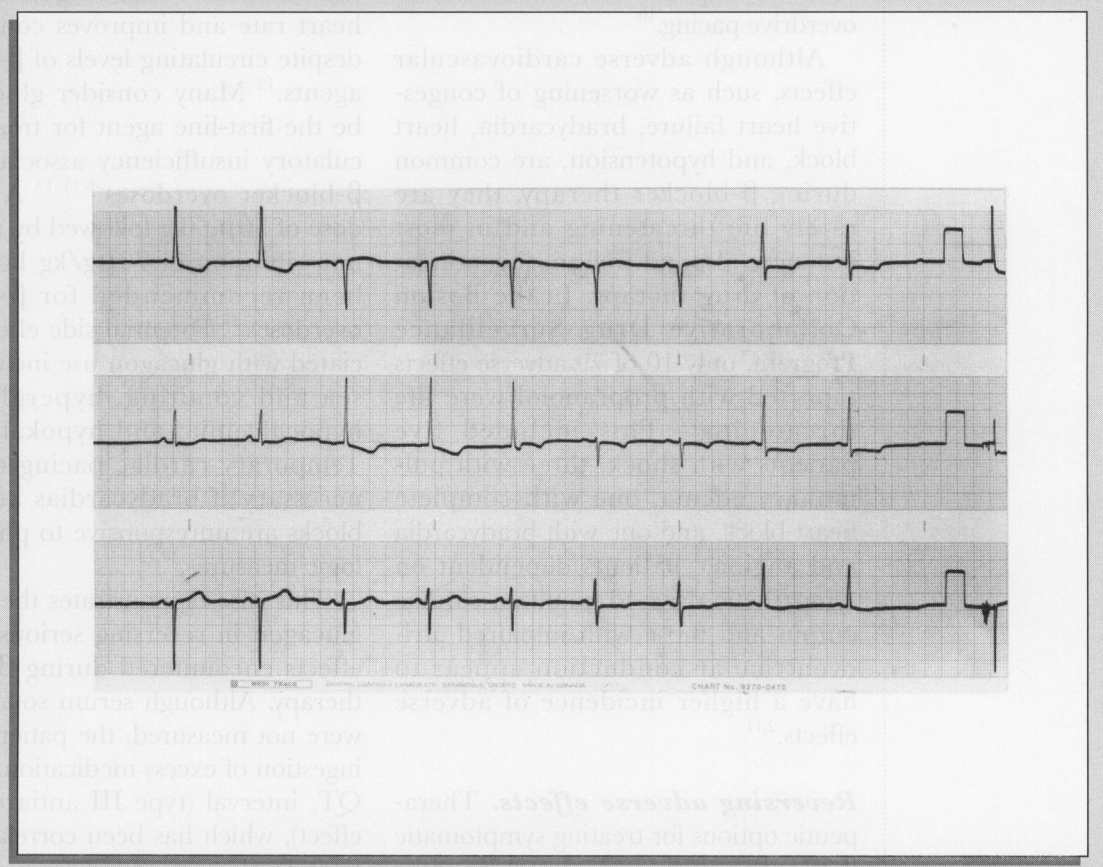
rhythm. An echocardiogram the following day showed mild left ventricular hypertrophy and mitral regurgitation. Electrophysiologic testing showed no evidence of a sick sinus syndrome and no requirement for a permanent pacemaker. Her electrocardiogram remained unchanged. Sotalol was discontinued, and the patient was discharged home with normal sinus rhythm.

Discussion

Sotalol is a non-selective β-blocker devoid of intrinsic sympathetic activity or membrane stabilization (local anesthetic) effects.[7] Although sotalol was first discovered in 1960, its antiarrhythmic properties and potential have only recently been realized.[8,9] The drug was approved in 1992 in the United States but has been available in Canada and Europe since 1974 for the treatment of angina, hypertension, and cardiac arrhythmias.[10] Sotalol is a unique antiarrhythmic agent with both class II (β-blocker) and class III (prolongation of cardiac repolarization) properties. Recent trials have shown sotalol to be effective in treating supraventricular tachycardia, in suppressing premature ventricular contractions and non-sustained ventricular tachycardia, and in terminating sustained ventricular tachycardia.[8]

Sotalol is rapidly absorbed; peak levels occur 2 to 4 hours after oral administration.[9] Bioavailability is nearly 100%, and protein binding is negligible.[9] There is no hepatic metabolism, and the drug is excreted primarily by the kidneys.[1,9] The apparent plasma half-life ranges from 7 to 15 hours and

Figure 2. **Standard 12-lead electrocardiogram following glucagon infusion**



is prolonged in the presence of renal insufficiency.[9]

Adverse effects. The most frequent adverse effects reported during controlled trials of sotalol for ventricular and supraventricular arrhythmias were dyspnea, bradycardia, fatigue, dizziness, and asthenia.[10] Although these side effects were common, only a few patients discontinued drug therapy. Bradycardia led to discontinuation of sotalol in 2.7% of patients.[10] Additional adverse effects included exacerbation of congestive heart failure in 1% of patients and proarrhythmic events manifested primarily by torsade de pointes in 1.9% of patients.[8,10] Risk factors associated with the development of torsade de pointes included a prolonged QT interval, bradycardia, and hypokalemia.[8,10] Half of the proarrhythmic events were self-limiting, and the remainder responded to treatment, such as intravenous magnesium sulfate, isoproterenol infusion, or overdrive pacing.[10]

Although adverse cardiovascular effects, such as worsening of congestive heart failure, bradycardia, heart block, and hypotension, are common during β-blocker therapy, they are rarely life threatening and in most instances respond well to discontinuation of drug therapy. In the Boston Collaborative Drug Surveillance Program, only 10 of 79 adverse effects reported with propranolol were life threatening.[2] This included five patients with shock, three with pulmonary edema, one with complete heart block, and one with bradycardia and angina.[2] Patients dependent on sympathetic drive to maintain cardiac output and those with impaired atrioventricular conduction appear to have a higher incidence of adverse effects.[2,11]

Reversing adverse effects. Therapeutic options for treating symptomatic β-blocker–induced bradycardias include atropine to reverse unopposed vagal activity, β-adrenergic stimulation, glucagon, and temporary cardiac pacing.[6,12,13] Atropine (0.5 to 2.0 mg intravenously) can be used to reverse the bradycardia of unopposed vagal activity.[12,13] Atropine, however, has been reported ineffective in reversing symptomatic bradycardia associated with β-blocker overdoses.[6]

Because β-blocking agents are competitive antagonists, infusion of β-adrenergic agonists, such as isoproterenol, can also be used to reverse effects of excessive β-blockade.[13] High doses of isoproterenol could be required, and unopposed β_2 stimulation can worsen associated hypotension.[13,14] A selective β_2-agonist, such as prenalterol, would be a better choice, but this drug is unavailable in North America.[14,15]

Glucagon has positive inotropic and chronotropic effects mediated by independent activation of the adenylate cyclase system through glucagon-specific receptors located in the myocardium.[3,12] Glucagon increases heart rate and improves contractility despite circulating levels of β-blocking agents.[12] Many consider glucagon to be the first-line agent for treating circulatory insufficiency associated with β-blocker overdoses.[6,11-13] A loading dose of 50 μg/kg followed by a continuous infusion of 70 μg/kg hourly has been recommended for β-blocker overdoses.[16] Potential side effects associated with glucagon use include nausea and vomiting, hyperglycemia, hypocalcemia, and hypokalemia.[6,13] Temporary cardiac pacing could be necessary if bradycardias and heart blocks are unresponsive to pharmacologic measures.[12,13]

This case demonstrates the value of glucagon in reversing serious adverse effects encountered during β-blocker therapy. Although serum sotalol levels were not measured, the patient denied ingestion of excess medication, and her QT_c interval (type III antiarrhythmic effect), which has been correlated with toxic levels, was within normal limits.[7] In addition, torsade de pointes, which has been a consistent feature of sotalol

intoxications reported to date, did not occur in this case.[7,17]

Unfortunately, the precipitating causes are unclear because electrophysiologic testing showed no evidence of a sick sinus syndrome. Dependence on underlying sympathetic tone to maintain an adequate heart rate could have been a contributing factor.[2,11]

Using glucagon to reverse adverse effects associated with β-blockade offers several advantages over atropine and isoproterenol, including avoidance of hypotension, better control of the end point by careful titration of the loading dose, and the availability of a continuous infusion drip to ensure persistent reversal of β-blockade. Continuous infusion is usually necessary in light of the 3- to 6-minute plasma half-life of glucagon.[16] However, this treatment was not used by our colleagues in the coronary care unit.

Vomiting is common and can be minimized by administering antiemetic agents.[6] All patients should be monitored for subsequent hyperglycemia, hypocalcemia, and hypokalemia. Large doses can produce urine discoloration from phenol contained in the packaged diluting solution.[4] Therefore, if large doses are required, dilution with 5% dextrose solution has been suggested.[4,13]

Conclusion

While the use of glucagon in β-blocker overdose has been reported, this case documents its efficacy in reversing adverse effects encountered during therapeutic use. ■

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